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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
DEVI, SARVAMANGALA J N	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 08/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/606,618	JUDD ET AL	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-7,17,18 and 21-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-7,17,18 and 21-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 June 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/22/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence reports (2 pages)*.

DETAILED ACTION

Election

1) Acknowledgment is made of Applicants' election filed 03/21/05, without prejudice, of invention II, claims 1-7 and 16-18, in response to the restriction requirement mailed 01/21/05. Applicants have further canceled the non-elected claims.

Applicants' Amendments

2) Acknowledgment is made of Applicants' preliminary amendments filed 05/18/05, 03/21/05 and 06/26/03. The amendment filed 05/18/05 is compliant.

Status of Claims

3) Claims 1, 8-16 and 19-20 have been canceled via the amendment filed 05/18/05.

Claims 2-7, 17 and 18 have been amended via the amendment filed 05/18/05.

New claims 21-29 have been added via the amendment filed 05/18/05.

Claims 2-7, 17, 18 and 21-29 are pending and are under examination.

Sequence Listing

4) The raw sequence listing filed in this application has been entered on 05/21/04.

Information Disclosure Statement

5) Acknowledgment is made of Applicants' Information Disclosure Statement filed 09/22/03. The information referred to therein has been considered and a signed copy is attached to this Office Action.

Priority

6) This application is a continuation of US application SN 09/994,192, filed 11/26/01, *now US patent 6,610,306*, which is a Continuation of application SN 09/177,039, filed 10/22/98, now abandoned.

Specification - Informalities

7) The specification of the instant application is objected to for the following reasons:

(a) The 'cross-reference to the related applications' on page 1 of the instant specification does not accurately reflect the current status of the parent application as indicated

above in italicized letters under 'priority'. Correction is requested.

(b) The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP 608.01(o).

(c) The limitation: 'polypeptide comprises amino acids 1 to 178 of SEQ ID NO: 4' in claims 7 and 29 does not have antecedent basis in the specification. Appropriate correction is required.

Double Patenting

8) The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970) and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 C.F.R 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R 3.73(b).

9) Claims 21, 3 and 6 are rejected under the judicially created doctrine of obviousness-type double patenting over claim 1 of the U.S. patent 6,610,306 (Applicants' IDS). Although the conflicting claims are not identical, they are not patentably distinct from each other because the product of claim 1 of the U.S. patent 6,610,306 falls within the scope of the instant claims.

Claims 4 and 5 are rejected under the judicially created doctrine of obviousness-type double patenting over claim 2 of the U.S. patent 6,610,306. Although the conflicting claims are not identical, they are not patentably distinct from each other because the product of claim 2 of the U.S. patent 6,610,306 falls within the scope of the instant claims.

Rejection(s) under 35 U.S.C. § 112, First Paragraph (New Matter)

10) Claims 21-23, 25 and those that depend from these claims are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

New base claims 21 and 25 include the recitation: polypeptide comprising ..... homolog thereof .... which .. induces antibodies to "*Neisseriae* strains" in a mammalian subject. New claim 25 includes the limitation: 'suitable detectable label or detection system'. New claim 22 includes the limitations: antibodies interfere with the binding of "said *Neisseriae* strains" to their cellular target. New claim 23 includes the limitations: antibodies are cross-reactive with "multiple *Neisseriae* strains". Applicants point to the original claim 1 as providing descriptive support for the new claim 21. However, the original claim 1 does not recite the broad limitation: "*Neisseriae* strains in a mammalian subject". Applicants point to the original claim 16 as providing descriptive support for the new claim 25. However, while the original claim 16 is supportive of a --suitable detectable label or detection system associated therewith--, it is not supportive of an independent unassociated suitable detectable label or detection system lacking association, as recited currently. Applicants point to the original claims and the specification at page 13, lines 15-18; page 15, lines 5-6 and 14-16; page 22, lines 25-27; page 20, line 24-page 21, line 4, and page 37 lines 13-19 as providing descriptive support for new claims 22 and 23. However, these parts of the specification do not provide support for a polypeptide as recited that induces antibodies which interfere with the binding of "said *Neisseriae* strains" to their cellular target and that are cross-reactive with "multiple *Neisseriae* strains", as recited currently. Therefore, the above-identified limitations in the claims are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to point to the descriptive support in the specification as filed, for the newly added limitation(s), or to remove the new matter from the

claim(s).

Rejection(s) under 35 U.S.C. § 112, First Paragraph (Written Description)

11) Claim 21, 25-27, 2, 3 and those dependent therefrom are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

It is noted that a polypeptide comprising at least eight consecutive amino acids from a 'homolog' of polypeptide of SEQ ID NO: 4 as recited in the instant claims does not exist independent of its function or activity, i.e., the ability to induce antibodies to *Neisseriae* strains in a mammalian subject such that it serves as an immunogenic or diagnostic composition and the ability to induce antibodies that are cross-reactive with multiple *Neisseriae* strains and that interfere with the binding of said *Neisseriae* strains to their cellular target. The claimed polypeptide homolog is recited as having one to four conservative amino acid replacements in SEQ ID NO: 4, or at least 85% identity with the amino acid sequence of SEQ ID NO: 4. The polypeptide homolog is intended for use as an immunogenic composition or as a diagnostic composition. However, the instant specification fails to teach a single such polypeptide homolog that concurrently has the biological activity identified above, such that the homolog composition when administered to a subject shows immunogenic activities or function(s), or diagnostic activity *in vitro*. Therapeutic or prophylactic and diagnostic applications minimally require an ability of the recited polypeptide homolog to interact specifically with an antibody. The precise structure or relevant identifying characteristics of each polynucleotide homolog molecule that encodes a homolog of the polypeptide of SEQ ID NO: 4 that is functional as recited in the claims, can only be determined empirically by actually making homolog DNA molecule that encodes the polypeptide homolog, and testing each varied DNA molecule to determine whether it encodes the recited polypeptide homolog functional as recited. The *Written Description Guidelines* state:

> There is an inverse correlation between the level of predictability in the art and the amount of disclosure necessary to satisfy the written description requirement. For example, if there is a well-established correlation between the structure and function in the art, one skilled in the art will be able to reasonably predict the complete structure of the claimed invention from its

function.

A mere statement that the invention includes a polypeptide 'homolog' of the amino acid of SEQ ID NO: 4 is insufficient to meet the adequate written description requirement of the claimed invention. The polypeptide of SEQ ID NO: 4 has specific biologic properties dictated by the structure of the protein and the corresponding structure of the structural gene sequence which encodes it. A convincing structure-function relationship has to exist between the structure of the gene sequence, the structure of the polypeptide or protein encoded, and the function of the encoded polypeptide or protein. The function cannot be predicted from the derivation or modification of the structure of the gene and in the instant case, the DNA comprising the modified nucleotides and encoding the recited polypeptide 'homolog' of SEQ ID NO: 4. Applicants have not shown that variation or modification of a reference sequence encoding a reference polypeptide or protein as claimed would automatically predict the production of a functional polypeptide homolog having the recited biologic activity. The specification fails to teach the structure or relevant identifying characteristics of a representative number of species of modified DNA molecules encoding the polypeptide homolog as recited, sufficient to allow one skilled in the art to determine that the inventors had possession of the invention as claimed. With the exception of the amino acid sequence species comprising SEQ ID NO: 4, a skilled artisan cannot envision the detailed chemical structure of all the at least 8 amino acid-long polypeptide homolog species of SEQ ID NO: 4 encompassed by the recited molecule. Regardless of the complexity or simplicity of the method of isolation, conception cannot be achieved until reduction to practice has occurred. Adequate written description requires more than a mere statement that it is a part of the invention and a reference to a potential method of isolating it. The nucleic acid comprising the modified nucleotides encoding the polypeptide homolog is required. See *Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993)* and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016*. The court held in *Univ. California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997) that: 'One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is' and that: 'A description of a genus of cDNAs (products) may be achieved by means of a recitation of a

representative number of cDNAs (products), *defined by nucleotide sequence*, falling in the scope of the genus or of a recitation of structural features common to the members of the genus, *which features constitute a substantial portion of the genus*. This is analogous to enablement of a genus under 112, (first paragraph) by showing the enablement of a representative number of species within the genus. See *Angstadt*, 537 F.2d at 502-503, 190 USPQ at 218'.

Rejection(s) under 35 U.S.C. § 112, First Paragraph (Scope of Enablement)

12) Claims 21-29, 2-7, 17 and 18 are rejected under 35 U.S.C § 112, first paragraph, because the specification, while being enabling for an immunogenic composition or a diagnostic composition comprising an isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 4, does not reasonably provide enablement for an immunogenic or diagnostic composition comprising an isolated or non-isolated polypeptide comprising at least eight consecutive amino acids from a 'homolog' of SEQ ID NO: 4 with or without containing one to four conservative amino acid replacements therein or with or without having at least 85% identity thereto, which induces antibodies to *Neisseriae* strains in a mammalian subject, or antibodies that interfere with the binding of *Neisseriae* strains to their cellular target, or antibodies that are cross-reactive with multiple *Neisseriae* strains as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Instant claims are evaluated based on the *Wands* analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

In the instant case, the nature of the invention is related to 'homologs' of a microbial polypeptide, or an immunogenic or diagnostic composition or a diagnostic kit comprising the same. The polypeptide comprising at least eight consecutive amino acids from a 'homolog'

thereof, with or without containing one to four conservative amino acid replacements therein or with or without having at least 85% identity thereto, is *required* to induce antibodies to *Neisseriae* strains in a mammalian subject, or antibodies that interfere with the binding of *Neisseriae* strains to their cellular target, or antibodies that are cross-reactive with multiple *Neisseriae* strains as claimed. The recited polypeptide 'homolog' is intended for use in an immunogenic composition, i.e., vaccine, or as a specific diagnostic reagent. The extent or degree of identity with the polypeptide having the amino acid sequence of SEQ ID NO: 4 is described to be at least 85% (see claims 3 and 27). However, there is no showing that such a polypeptide 'homolog' retains the antigenic, immunogenic or protective and diagnostic functions. Although a microbial polypeptide such as the one having SEQ ID NO: 4 is expected in the art to generally induce specific antibodies, the ability of undefined 'homologs' of such a polypeptide as recited to serve as an immunogenic composition having the ability to induce antibodies to *Neisseriae* strains in a mammalian subject, or antibodies that interfere with the binding of *Neisseriae* strains to their cellular target, or antibodies that are cross-reactive with multiple *Neisseriae* strains, or to serve as a diagnostic reagent/kit, is not predictable. The instant specification fails to teach how to produce a 'homolog' having at least 85% identity with the sequence of SEQ ID NO: 4 or one to four conservative amino acid replacements therein such that it is capable of serving as an immunogenic composition with the ability to induce to *Neisseriae* strains in a mammalian subject, or antibodies that interfere with the binding of *Neisseriae* strains to their cellular target, or antibodies that are cross-reactive with multiple *Neisseriae* strains, or to serve as a diagnostic reagent/kit. The specification provides no guidance as to which specific amino acids must be retained in the polypeptide 'homolog' and which may be varied without causing detrimental effects to the claimed polypeptide product that is meant to serve as an immunogenic composition or a diagnostic composition. There is no guidance in the instant specification with regard to which amino acid variations, i.e., insertions, deletions, additions and substitutions, in the polypeptide would result in a 'homolog' polypeptide that would retain the functional integrity or biological, antigenic and immunogenic competence of the native polypeptide, without rendering it non-functional. This is important because the art reflects unpredictability as to which amino acids in a specific protein can be varied, i.e., replaced or added, without adversely affecting the functional properties of that specific protein. While it is known in the art that variation in one or

more amino acids is possible in a given protein, the exact position within its amino acid sequence where replacements or variations can be made, with a reasonable expectation of success of retaining the protein's or polypeptide's functional competence, is not certain. A random replacement affecting the epitopic amino acid positions that are critical, for example, to the three-dimensional conformational structure and specific binding property of the protein, would result in a polypeptide that may be non-functional, or not optimally antigenic as a diagnostic reagent, or not optimally immunogenic as a vaccine candidate, because such positions tolerate no or little modifications. For instance, Houghten *et al.* (New Approaches to Immunization, *Vaccines86*, Cold Spring Harbor Laboratory, p. 21-25, 1986 – Applicants' IDS) teach the criticality of individual amino acid residues and their positions in peptide antigen-antibody interactions. Houghten *et al.* state (see page 24):

> One could expect point mutations in the protein antigen to cause varying degrees of loss of protection, depending on the relative importance of the binding interaction of the altered residue. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool.

Thus, the art reflects that variations in critical residues at specific positions in an amino acid sequence could result in a polypeptide which may induce an antibody that may not recognize or bind to the native polypeptide of a microorganism. In the instant case, this is important because the recited homolog in the claimed composition is recited as having as much as 25% dissimilarity with the amino acid sequence of SEQ D NO: 4 and yet is required to remain biologically, immunogenically or diagnostically active. The instant disclosure lacks guidance on the precise position(s), nature and extent of amino acid replacements, deletions or variations that can be made in the claimed polypeptide in order to produce a 'homolog', and with regard to whether it would serve as an effective immunogen capable of inducing antibodies to the broadly recited *Neisseriae* strains in a mammalian subject, or antibodies that interfere with the binding of *Neisseriae* strains to their cellular target, or antibodies that are cross-reactive with multiple *Neisseriae* strains, and of serving as a diagnostic reagent/kit. If one made such 85% identical homologs of the polypeptide of SEQ ID NO: 4, there is no guarantee or predictability that the resultant polypeptide homologs having 25% dissimilarity thereto would retain the biological, immunogenic and/or diagnostic integrity of the native polypeptide of SEQ ID NO: 4. It is highly

unlikely that such a polypeptide homolog having 25% dissimilarity to SEQ ID NO: 4 would even remain *Neisseriae*-specific. Skolnick *et al.* (*Trends in Biotechnology* 18: 34-39, 2000) taught that a skilled artisan is well aware that assigning functional activities for any particular protein or a family of proteins based upon sequence homology is inaccurate, partly because of the multifunctional nature of proteins (see abstract; and page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see abstract and Box 2). Furthermore, even with regard to conservative amino acid replacements within a protein, the state of the art documents functional unpredictability. For instance, Lazar *et al.* (*Mol. Cellular Biol.* 8: 1247-1252, 1988 – Applicants' IDS) demonstrated that a substitution of Leu with a conservative amino acid residue, such as, Ile or His in the transforming growth factor (TGF) alpha led to a mutant protein with dramatically altered biological activities. Lazar *et al.* stated that they 'did not expect that a mutation of Leu to Ile (which have similar sizes and polarities) would cause such a strong effect'. See paragraph bridging left and right columns on page 1251; and third full paragraph on page 1251. Lazar *et al.* also taught that in transforming growth factor alpha, replacement of aspartic acid at position 47 with a conservative amino acid, glutamic acid, sharply reduced the biological activity of the mitogen. Clearly, the specification lacks adequate guidance and disclosure that would limit the experimentation from being undue. Given the art-recognized unpredictability associated with the structure-function relationship of polypeptide, one of skill in the art would look into the specification for specific teaching and guidance, which in the instant case is lacking. Due to the lack of specific disclosure as to the precise structure of polypeptide 'homologs'; the lack of demonstration of antigenic, immunogenic, diagnostic and/or protective ability of such 'homologs', the art-recognized unpredictability factor associated with the retention of functions of the native polypeptide following amino acid replacements; the breadth of the claims; and the quantity of experimentation necessary, undue experimentation would have been required to practice the invention as claimed. The claims are viewed as not meeting the scope of enablement provisions of 35 U.S.C. § 112, first paragraph.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

13) The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his/her invention.

14) Claims 21-29, 2-7, 17 and 18 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claims 21, 25-27, 2 and 3 are vague and indefinite in the recitation 'homolog', because it is unclear what is encompassed in this limitation. What constitutes a 'homolog' and how much of the polypeptide's original structure has to be retained such that the resulting product qualifies as a 'homolog' is not clear. The metes and bounds of the structure encompassed in the limitation 'homolog' are indeterminate. It is further unclear whether the 'homolog' recited in claims 21 and 25 is a structural homolog or a functional homolog of the at least eight amino acid-long polypeptide from SEQ ID NO: 4.

(b) Claim 21 is vague and indefinite in the recitation 'effective amount' because it is a relative term. The term 'effective' is not specifically defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably appraised of the scope of the claim. What amount qualifies as an 'effective' amount, and in what capacity the amount is 'effective', i.e., prophylactically effective, therapeutically effective, or immunogenically effective etc., is unclear.

(c) Claims 2 and 25 are vague and indefinite in the limitation 'SEQ ID NO: 4' without particularly reciting that it is --the amino acid sequence of SEQ ID NO: 4--.

(d) Claims 3 and 27 are vague and indefinite in the limitation: '85% identity', because it is unclear whether this represents sequence (structural) identity or functional identity.

(e) Claims 3 and 27 are vague and indefinite in the limitation 'the sequence of SEQ ID NO: 4' without particularly reciting that it is --the amino acid sequence of SEQ ID NO: 4--.

(f) Claim 5 is vague and indefinite in the recitation 'fragment' (see line 2), because it is unclear what is encompassed in this limitation. What constitutes a 'fragment' and how much of the second polypeptide's or protein's original structure has to be retained such that the resulting product qualifies as a 'fragment' is not clear. The metes and bounds of the structure encompassed in the limitation 'fragment' are indeterminate. Does a single amino acid qualify as a 'fragment'?

(g) Claims 2-7, 17, 18, 21-24 and 26-29, which depend directly or indirectly from claim 21 or 25, are also rejected under 35 U.S.C. § 112, second paragraph, as being indefinite, because of the indefiniteness or vagueness, identified above in the base claim.

Rejection(s) under 35 U.S.C. § 102

15) The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office Action:

> A person shall be entitled to a patent unless –
> **(b)** the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16) Claims 21-24 and 2-7 are rejected under 35 U.S.C § 102(a) as being anticipated by Manning *et al.* (*Microb. Pathogenesis*. 25: 11-22, July 1998 - Applicants' IDS) (Manning *et al.*, 1998) in light of Richarme *et al.* (*Ann. Microbiol.* 133A: 199-204, 1982 – Applicants' IDS).

It is noted that the authorship of Manning *et al.* (1998) and the inventorship of the instant application are non-identical.

Manning *et al.* (1998) taught an isolated outer membrane protein (i.e., Omp85 polypeptide) of *N. meningitidis* having comprising the 797 amino acid-long amino acid sequence with the Genebank accession No. AF021245 that has 100% sequence identity with the instantly recited SEQ ID NO. 4 of the instant invention. See especially Figure 5 and abstract of Manning *et al.* (1998) and the attached sequence with the Genebank accession No. AF021245. The protein taught by Manning *et al.* (1998) is a recombinant protein, or a fusion protein fused to a second polypeptide such as MBP or maltose binding protein. See page 15; 'Materials and Methods'; and page 20 under 'Production of a MBP/Omp85 fusion protein'. A composition (i.e., immunogenic composition) comprising 0.1 to 1.0 mg of the purified MBP/Omp85 contained in an adjuvant (i.e., pharmaceutically acceptable carrier) for use in an immunization procedure is taught. See page 20, right column, first full paragraph. The Neisserial Omp85 proteins are believed to be important immunological targets of the host immune response (see first paragraph under 'Conclusions'). Manning *et al.* (1998) taught that the meningococcal Omp85 protein is 95% identical to the gonococcal Omp85 (see page 15, left column; and Figure 2), and thus Manning *et al.* (1998) taught a homologue polypeptide of the instantly recited SEQ ID NO: 4

that has at least 85% identity to SEQ ID NO: 4 or that contains conservative amino acid amino acid replacements as recited. Manning *et al.* (1998) further taught that Omp85 homologues are identified in all of the commensal neisserial species tested and that the Omp85 protein is conserved among all the neisserial species (see paragraph bridging pages 15 and 16; and Figure 6), thus indicating the inherent ability of the prior art polypeptide to induce antibodies cross-reactive with multiple *Neisseriae* strains. That maltose binding protein fusion partner taught by Manning *et al.* is an antigen from a heterologous pathogenic species is inherent from the teaching of Manning *et al.* in light of what is well known in the state of the art. For instance, Richarme *et al.* taught the source of maltose binding protein to be *E. coli* bacteria (see abstract). The ability to induce antibodies

The teachings of Manning *et al.* anticipate the instant claims. Richarme *et al.* is **not** used as a secondary reference in combination with Manning *et al.*, but rather is used to show that every element of the claimed subject matter is disclosed by Manning *et al.*, because Richarme *et al.* teach maltose binding protein to be of *E. coli* (heterologous species) origin. See *In re Samour* 197 USPQ 1 (CCPA 1978).

Claims 21-24 and 2-7 are anticipated by Manning *et al.*

17) Claims 21-26, 2, 4, 5, 17 and 18 are rejected under 35 U.S.C § 102(b) as being anticipated by Chong *et al.* (WO 94/12641) ('641) as evidenced by Harlow *et al.* (*In*: *Antibodies*: *A laboratory Manual.* Cold Spring Harbor Laboratory, Chapter 5, p. 76, 1988), Piwnica-Worms (US 6,348,185) or *Protein Sequences on STN* (page 12).

It is noted that the limitation 'homolog' in the independent claims do not have a structure or size limit.

The transitional limitations 'having', 'comprising', 'including', 'containing', or 'characterized by,' represent open-ended claim language and therefore, do not exclude additional, unrecited elements. See MPEP 2111.03 [R-1]. See *Moleculon Research Corp. v. CBS, Inc., 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986)*; *In re Baxter, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981)*; *Ex parte Davis, 80 USPQ 448, 450 (Bd. App. 1948)* ('comprising' leaves 'the claim open for the inclusion of unspecified ingredients even in major amounts'). Therefore, the limitation 'comprising' or 'contains' in the instant claim(s) allows additional amino acid residues to be present on one or either side of the recited polypeptide, or a homolog

thereof. It should be noted that the transitional phrase 'consisting of' excludes any element, step, or ingredient not specified in the claim. *In re Gray, 53 F.2d 520, 11 USPQ 255 (CCPA 1931)*; *Ex parte Davis, 80 USPQ 448, 450 (Bd. App. 1948)* ('consisting of' defined as 'closing the claim to the inclusion of materials other than those recited except for impurities ordinarily associated therewith.').

Chong *et al.* disclosed an isolated and purified 27 amino acid-long fragment, SEQ ID NO: 35, or a synthetic peptide of the D-15 polypeptide fused to a heterologous protein, such as, glutathione S-transferase, i.e., second heterologous polypeptide. The prior art polypeptide comprises the sequence, DGVSLGGN, of which DGVSLG is 100% identical to amino acids 481-486 of the instantly claimed polypeptide of SEQ ID NO: 4. See Table 2 of Chong *et al.* The amino acids glycine and asparagine occurring at the end of the DGVSLG prior art sequence represent two conservative amino acid replacements of tyrosine and asparatic acid in the eight amino acid-long sequence of DGVSLGYD found at positions 480-488 of the instantly recited SEQ ID NO: 4. Therefore, the prior art polypeptide of SEQ ID NO: 35 is viewed as a 'homolog' of the instantly recited SEQ ID NO: 4. The polypeptide sequence is present in a physiologically acceptable carrier, and is highly immunogenic and elicits protective antibodies in a rabbits upon immunization with 50 to 200 micrograms in Freund's complete adjuvant (i.e., immunogenic composition). The polypeptide is useful as diagnostic antigen for the purpose of diagnosis and is used in ELISA, RIAs and other antibody binding assays or procedures known in the art. A diagnostic kit comprising the polypeptide sequence is taught. See abstract; claims 13, 20, 21-23 and 28-31; SEQ ID NO. 35 in Table 2; paragraph bridging pages 3 and 4; paragraph bridging pages 5 and 6; first and second full paragraphs on page 6; Figures 9, 10 and 16; section iii on pages 12 and 13; sections vii, viii, ix-xiv; Examples 12 and 15; section 2 on page 31; and pages 24-28. The antibodies induced by Chong's isolated and purified 27 amino acid-long fragment, SEQ ID NO: 35, or the fusion protein thereof, contained in a physiologically acceptable carrier, are expected to have the functional properties recited in the instant claims, i.e., reactivity with *Neisseria* strains, cross-reactivity with multiple *Neisseria* strains, and interference with the binding of *Neisseria* strains to their cellular target. The art recognizes that the smallest peptide which elicits antibodies that bind to the original full length protein is 6 amino acids in length (see first sentence under 'Size of the Peptide' on page 76 of Harlow *et al.*), and the six amino acid-

long DGVSLG sequence from the instantly recited SEQ ID NO: 4 is contained in the prior art polypeptide. That the prior art polypeptide diagnostic antigen used in ELISA, RIAs and other antibody binding assays or procedures known in the art, contains a detection system or detectable label is inherent from the teachings of Chong *et al.*

That asparagine and aspartic acid as well as glycine and tyrosine are functionally similar or conservative amino acids is well known in the art. For instance, see the attached page 12 of the '*Protein Sequences of STN*' and paragraph bridging columns 15 and 16 of Piwnica-Worms.

The teachings of Chong *et al.* anticipate the instant claims. Harlow *et al.*, the disclosure from '*Protein Sequences of STN*' or Piwnica-Worms is **not** used as a secondary reference in combination with Chong *et al*, but rather is used to show that every element of the claimed subject matter is disclosed by Chong *et al.* with the unrecited limitation(s) being inherent in view of what is known in the art as explained above. See *In re Samour* 197 USPQ 1 (CCPA 1978).

Claims 21-26, 2, 4, 5, 17 and 18 are anticipated by Chong *et al.*

Rejection(s) under 35 U.S.C. § 103

18) The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth In this Office action:

> **(a)** A patent may not be obtained though the invention is not identically disclosed or described as set forth In section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person. having ordinary skill In the art to which said subject matter pertains. Patentability shall not be negatived by the manner In which the invention was made.

The factual inquiries set forth In *Graham v. John Deere Co.*, 148 USPQ 459, that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill In the pertinent art.
4. Considering objective evidence present In the application indicating obviousness or unobviousness.

19) Claims 25-29, 17 and 18 are rejected under 35 U.S.C § 103(a) as being unpatentable over Manning *et al.* (*Microb. Pathogenesis.* 25: 11-22, July 1998 - Applicants' IDS) (Manning *et al.*, 1998).

The teachings of Manning *et al.* (1998) are described above which do not teach their polypeptide-comprising composition to be a diagnostic composition, reagent or kit which further comprises a detectable label.

However, methods of assembling a diagnostic kit, composition or reagent using an art-disclosed product and an art-known detectable label, such as a radiolabel, enzyme label or fluorescent label, was well known and routinely practiced in the art at the time of the invention, and was well within the realm of routine experimentation.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce a diagnostic composition, reagent or kit for the *in vitro* diagnosis of *Neisseriae* infection by assembling together an art-known detectable label and the specific polypeptide of Manning *et al.* (1998) to produce the instant invention with a reasonable expectation of success. One of skill in the art would have been motivated to produce the instant invention for the expected benefit of making readily available Manning's (1998) polypeptide or for commercializing Manning's (1998) polypeptide for diagnostic use, since Manning *et al.* (1998) explicitly taught that the polypeptide is cross-reactive or conserved being present in different species of *Neisseriae*.

Claims 25-29, 17 and 18 are *prima facie* obvious over the prior art of record.

Relevant Art

20) The prior art made of record and not relied upon in any of the rejections is considered pertinent to Applicants' disclosure:

- Kawarabayasi *et al.* (*DNA Res.* 5: 55-76, 1998) taught a polypeptide comprising the eight amino-long sequence, LGYDVYGK, which shows 100% match with amino acid residues 485 to 492 of the instantly recited SEQ ID NO: 4. See the attached sequence alignment report.

- Albertini *et al.* (*J. Bacteriol.* 173: 3573-3579, 1991) taught a polypeptide comprising the eight amino-long sequence, PNAETKTV, which shows 100% match with amino acid residues 328 to 335 of the instantly recited SEQ ID NO: 4. See the attached sequence alignment report.

Remarks

21) Claims 2-7, 17, 18 and 21-29 stand rejected.

22) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The central Fax number for submission of amendments, responses and papers is (571) 273-8300.

23) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

24) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system. A message may be left on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

July, 2005

S. DEVI, PH.D.
PRIMARY EXAMINER

O30912

ID O30912 PRELIMINARY; PRT; 797 AA.

SEQ ID NO. 4

AC O30912;
DT 01-JAN-1998 (TrEMBLrel. 05, Created)
DT 01-JAN-1998 (TrEMBLrel. 05, Last sequence update)
DT 01-MAR-2004 (TrEMBLrel. 26, Last annotation update)
DE Outer membrane protein Omp85.
GN Name=omp85;
OS Neisseria meningitidis.
OC Bacteria; Proteobacteria; Betaproteobacteria; Neisseriales;
OC Neisseriaceae; Neisseria.
OX NCBI_TaxID=487;
RN [1]
RP SEQUENCE FROM N.A.
RC STRAIN=HH;
RX MEDLINE=98379445; PubMed=9705245; DOI=10.1006/mpat.1998.0206;
RA Manning D.S., Reschke D.K., Judd R.C.;
RT "Omp85 proteins of Neisseria gonorrhoeae and Neisseria meningitidis
RT are similar to Haemophilus influenzae D-15-Ag and Pasteurella
RT multocida Oma87.";
RL Microb. Pathog. 25:11-21(1998).
DR EMBL; AF021245; AAC17599.1; -.
DR InterPro; IPR000184; Bac_surfAg_D15.
DR InterPro; IPR010827; Surf_Ag_VNR.
DR Pfam; PF01103; Bac_surface_Ag; 1.
DR Pfam; PF07244; Surf_Ag_VNR; 5.
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SEQ ID NO. 4
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R;Albertini, A.M.; Caramori, T.; Crabb, W.D.; Scoffone, F.; Galizzi, A.
J. Bacteriol. 173, 3573-3579, 1991
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R;Kunst, F.; Ogasawara, N.; Moszer, I.; Albertini, A.M.; Alloni, G.; Azevedo, V.; Bertem
C.; Bron, S.; Brouillet, S.; Bruschi, C.V.; Caldwell, B.; Capuano, V.; Carter, N.M.; Cho
A.; Ehrlich, S.D.; Emmerson, P.T.; Entian, K.D.; Errington, J.; Fabret, C.; Ferrari, E.
Nature 390, 249-256, 1997
A;Authors: Foulger, D.; Fritz, C.; Fujita, M.; Fujita, Y.; Fuma, S.; Galizzi, A.; Galler
iech, J.; Harwood, C.R.; Henaut, A.; Hilbert, H.; Holsappel, S.; Hosono, S.; Hullo, M.F.
Koetter, P.; Koningstein, G.; Krogh, S.; Kumano, M.; Kurita, K.; Lapidus, A.; Lardinois,
A;Authors: Lauber, J.; Lazarevic, V.; Lee, S.M.; Levine, A.; Liu, H.; Masuda, S.; Maueel
Y, M.; Ogawa, K.; Ogiwara, A.; Oudega, B.; Park, S.H.; Parro, V.; Pohl, T.M.; Portetelle
Rieger, M.; Rivolta, C.; Rocha, E.; Roche, B.; Rose, M.; Sadaie, Y.; Sato, T.; Scanlon,
A;Authors: Schleich, S.; Schroeter, R.; Scoffone, F.; Sekiguchi, J.; Sekowska, A.; Seror
akeuchi, M.; Tamakoshi, A.; Tanaka, T.; Terpstra, P.; Tognoni, A.; Tosato, V.; Uchiyama,
T.; Winters, P.; Wipat, A.; Yamamoto, H.; Yamane, K.; Yasumoto, K.; Yata, K.; Yoshida, K
A;Authors: Yoshikawa, H.F.; Zumstein, E.; Yoshikawa, H.; Danchin, A.
A;Title: The complete genome sequence of the Gram-positive bacterium Bacillus subtilis.
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R;Kawarabayasi, Y.; Sawada, M.; Horikawa, H.; Haikawa, Y.; Hino, Y.; Yamamoto, S.; Sekine
M.; Ohfuku, Y.; Funahashi, T.; Tanaka, T.; Kudoh, Y.; Yamazaki, J.; Kushida, N.; Oguchi,
DNA Res. 5, 55-76, 1998
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